REMARKS

Claims 1, 3-22, and 31 are pending in the subject application. Claims, 1, 11, and 18 have been amended by the present communication. Supports for the amendments can be found throughout the specification, and no new matter is added.

Supports for the currently amended claim 1 can be found, for example, at paragraphs [0005] on pages 3-4, and [0007] on pages 5-6 of the amended specification in the second preliminary amendment filed June 21, 2007.

Supports for the currently amended claim 18 can be found, for example, at paragraphs [0009] on page 7, and [0013] on pages 8-9 of the amended specification in the second preliminary amendment filed June 21, 2007.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 3, 10-11, 16-17, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622). Applicants respectfully traverse this rejection.

Specifically, the Examiner states the following:

> "With regard to claim 1, Wong teaches a method for producing DNA, wherein a methylation analysis is used, comprising the step of: a) performaing a genome-wide amplification on genomic DNA (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p.2620. col. 1), and b) using the amplificates generated in step a) as a standard in the methylation analysis (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction)."
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> Lines 13-18, page 3 of Office Action dated July 22, 2010

"[A]nticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Systems, Inc. v. Kent State University*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). "Anticipation requires identity of invention. The claimed invention, as described in

appropriately construed claims, must be the same as that of the reference in order to anticipate." *Glaverbel Societe Anonyme v. Northlake Marketing & Supply Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995).

"To be a prior art under section 102(b), the reference must put the anticipating subject matter at issue into the possession of the public through an enabling disclosure." *Chester v. Miller*, 906 F.2d 1574, 1577, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990) (citations omitted). "To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. 'A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.'" *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research,* 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (citations omitted).

Applicants respectfully submit that Wong *et al.* fails to teach or suggest using amplificates of the genomic DNA "**as a non-methylated standard in the methylation analysis over a linear range**." Although the Examiner asserts that Wong *et al.* teaches that amplified products were used in methylation specific PCR reaction, Applicants submit that the disclosure of Wong *et al.* does not enable those skilled in the art to perform methylation analysis using amplificates of genomic DNA "**as a non-methylated standard**" in the methylation analysis "**over a linear range**" as recited in claim 1.

In addition, the Examiner made comments regarding the phrase "standard" recited in claim 1, stating that:

> "Furthermore, while Applicant argues that Wong does not teach the use of amplificates as "standards," the claim does not clearly establish how a sample is used as a standard. ... Next, it is clearly shown that the products of the amplification were used in further methylation analysis and also that samples were also included as controls for both methylated DNA and unmethylated DNA (see p. 2620, col. 2 and Figure 1A and B). Therefore, in the absence of limitations in the claims which clearly distinguish over the teachings of Wong, the rejections are maintained."
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> Line 15 on page 13 to line 4 on page 14 of the Office Action dated July 22, 2010.

Without acquiescing to the Examiner's assertion and to expedite the prosecution of the claimed invention, claim 1 has been amended to recite the phrase "**as a non-methylated standard in the methylation analysis over a linear range**." Applicants submits that the controls in Wong *et al.* does not provide an enabling disclosure for this feature of the currently amended claim 1. Further, Wong *et al.* only teaches the use of PEP to amplify genomic DNA for about 60 folds in order to reduce the amount of genomic DNA needed for subsequent assays, where the claimed invention can perform a more than 5,000 fold genome-wide amplification.

Since Wong *et al.* fails to disclose or suggest each and every element of the amended claim 1, and Wong *et al.* does not provide an enabling disclosure to perform methylation analysis using amplificates of genomic DNA "as a non-methylated standard in the methylation analysis over a linear range" as recited in the currently amended claim 1, Wong *et al.* cannot anticipate the claimed invention. Accordingly, withdrawal of the anticipation rejection over Wong *et al.* is respectfully requested.

Claims 18-22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Adorjan *et al.* (Nucleic Acids Research, 2002, 20(5):e21, p1-9). Applicants respectfully traverse this rejection.

Specifically, the Examiner states the following:

> "With regard to claim 18, Adorjan teaches a method for the determination of methylation rates of DNA samples by means of microarrays containing CG and TG oligomers, comprising the steps of:
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> a) hybridizing the arrays with two calibration standards, which have defined methylation rates (p.2, col. 2, where for each analyzed CpG position, CG and TG oligomers are spotted onto a glass array; Table 1, p.3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1);
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> b) using the hybridization values of step a) to determine a calibration curve for use as a suitable method of calculation (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3, col. 2); and
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> c) determining the actual methylation rates of the investigated DNA samples by using this prepared calibration curve (Figure 1, where the amount of

> methylation is calculated based on the hybridization and calibration on the array, see p. 3, col. 2)."
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> Lines 8-20, page 5 of Office Action dated July 22, 2010

Claim 18 has been amended to recite the phrase "absolute methylation rates" and "wherein one calibration standard comprises non-methylated DNA and the other calibration standard comprises specifically methylated DNA." Applicants respectfully submit that Adorjan *et al.* does not disclose or suggest these features of the currently amended claim 18. In particular, paragraph [0013] on pages 8-9 of the amended specification in the second preliminary amendment filed June 21, 2007, provides that the teaching of Adorjan *et al.* is limited to "relative" estimations of methylation analysis. On the other hand, the claimed invention provides measurements of "absolute" methylation rates or "true" methylation rates.

In addition, Applicants respectfully submits that Adorjan *et al.* fails to provide an enabling disclosure for "absolute methylation rates" or measurement of "absolute methylation rates" using calibration standards "wherein one calibration standard comprises non-methylated DNA and the other calibration standard comprises specifically methylated DNA."

Since Adorjan *et al.* fails to disclose or suggest each and every element of the currently amended claim 18, and Adorjan *et al.* does not provide an enabling disclosure to measure "absolute methylation rates" or "wherein one calibration standard comprises non-methylated DNA and the other calibration standard comprises specifically methylated DNA" as recited in the currently amended claim 18, Adorjan *et al.* cannot anticipate the claimed invention. Accordingly, withdrawal of the anticipation rejection over Adorjan *et al.* is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claim 12 is rejected under 35 U.S.C. § 103(a) as being obvious over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) in view of Adorjan *et al.* (Nucleic Acids Research, 2002, 20(5):e21, p1-9). Applicants respectfully traverse this rejection.

In particular, the Examiner states the following:

> "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success. As taught by Adorjan, 'We have developed the first microarray-based technique which allows genome-wide assessment of selected CpG dinucleotides as well as quantification of methylation at each site. Several hundred CpG sites were screened in 76 samples from four different human tumour types and corresponding healthy controls. Discriminative CpG dinucleotides were identified for different tissue type distinctions are used to predict the tumour class of as yet known samples with high accuracy using machine leaning techniques.' Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success."
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> Lines 3-15, page 8 of the Office Action dated July 22, 2010

A claimed invention may be invalid if it is obvious in view of a combination of elements taken from the prior art: "A combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). To ascertain whether an invention is obvious, a set of factors known as the "Graham factors" originally set out by the Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) are considered: (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) any secondary considerations such as commercial success or long-felt but unsolved need.

"*Graham* is interpreted as continuing to place the 'burden of proof on the Patent Office which requires it to product the factual basis for its rejection of an application under sections 102 and 103.'" *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). A *prima facie* case is typically established by a motivation to combine the references and a reasonable expectation of success to one of ordinary skill in the art. "Where claimed subject matter has been rejected as obvious in view of a combination of prior-art references, a proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art

would also have revealed that, in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Claim 12 is a dependent claim of the currently amended claim 1. As discussed above, neither Wong *et al.* nor Adorjan *et al.* discloses or suggests each and every element of the currently amended claim 1. Applicants respectfully submit that the combination of Wong *et al.* and Adorjan *et al.* still fails to disclose or suggest each and every element of the currently amended claim 1. Thus, the Examiner has not established a *prima facie* obviousness case for the currently amended claim 1, and therefore not for claim 12 either. Accordingly, withdrawal of the obviousness rejection over the combination of Wong *et al.* and Adorjan *et al.* is respectfully requested.

Claim 13 is rejected under 35 U.S.C. § 103(a) as being obvious over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) in view of Tost *et al.* (Nucleic Acids Research, 2003, 31(9):e50, p1-10). Applicants respectfully traverse this rejection.

In particular, the Examiner states the following:

> "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success. As taught by Tost, 'Calibration curves were recorded for simplex, duplex and triplex analysis. For multiplex analysis only extension primers were chosen that did not overlap in their sequence.' Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success."
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> Lines 3-15, page 8 of the Office Action dated July 22, 2010

Claim 13 is a dependent claim of the currently amended claim 1. Applicants submit that the Examiner relies on Tost *et al.* for the teaching of multiplex amplification. As discussed above, Wong *et al.* fails to disclose or suggest each and every element of the currently amended claim 1, and combination with Tost *et al.* cannot cure the defect of Wong

et al. Thus, the Examiner has not established a *prima facie* obviousness case for the currently amended claim 1, and therefore not for claim 13 either. Accordingly, withdrawal of the obviousness rejection over the combination of Wong *et al.* and Tost *et al.* is respectfully requested.

Claims 14-15 are rejected under 35 U.S.C. § 103(a) as being obvious over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) in view of Guilleret *et al.* (Int. J. Cancer, 2002, 101: 335-341). Applicants respectfully traverse this rejection.

In particular, the Examiner states the following:

> "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the mixture of methylated an non-methylated DNA as a standard as taught by Guilleret to arrive at the claimed invention with a reasonable expectation for success. While Wong teaches the use of methylated controls and unmethylated controls, Wong does not teach the controls for detection of different types of methylation, such as differential methylation. As taught by Guilleret, 'Unmethylated an methylated plasmids were mixed at different ratios. The bisulfite modification was performed on fully methylated and unmethylated plasmids as well as on different mixes.' (p. 336, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the mixtures of methylated and non-methylated DNA as a standard as taught by Guilleret to arrive at the claimed invention with a reasonable expectation for success."
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> Lines 3-15, page 8 of the Office Action dated July 22, 2010

Claims 14 and 15 are dependent claims of the currently amended claim 1. Applicants submit that the Examiner relies on Guilleret *et al.* for the teaching of mixtures of methylated and non-methylated DNA as a standard. As discussed above, Wong *et al.* fails to disclose or suggest each and every element of the currently amended claim 1, and combination with Guilleret *et al.* cannot cure the defect of Wong *et al.* Thus, the Examiner has not established a *prima facie* obviousness case for the currently amended claim 1, and therefore not for claims 14 and 15 either. Accordingly, withdrawal of the obviousness rejection over the combination of Wong *et al.* and Guilleret *et al.* is respectfully requested.

Claims 4-7 are rejected under 35 U.S.C. § 103(a) as being obvious over Wong *et al.* (Cancer Research, 1997, vol. 57: 2619-2622) in view of Apgar *et al.* (Human Immunology, 2003, 64(10), Suppl. 1, p. S86 Abstract). Applicants respectfully traverse this rejection.

In particular, the Examiner states the following:

> "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made ... to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success. As taught by Apgar, 'replicate aliquots of dilute DNA were amplified by MDA using a GenomiPhi kit.' (Abstract, line 10). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated ... to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success."
>
> Lines 3-15, page 8 of the Office Action dated July 22, 2010

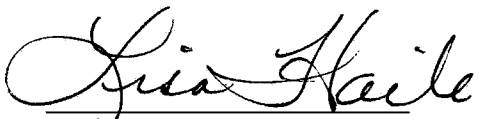
Claims 4-7 are dependent claims of the currently amended claim 1. Applicants submit that the Examiner relies on Apgar *et al.* for the teaching of the GenomiPhi kit. As discussed above, Wong *et al.* or any other cited reference, fails to disclose or suggest each and every element of the currently amended claim 1, and combination with Apgar *et al.* cannot cure the defect of Wong *et al.* or any other cited reference. Thus, the Examiner has not established a *prima facie* obviousness case for the currently amended claim 1, and therefore not for claims 4-7 either. Accordingly, withdrawal of the obviousness rejection over the combination of Wong *et al.* and Apgar *et al.* is respectfully requested.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

The Commissioner is hereby authorized to charge $555 as payment for the Petition for the Three-Month Extension of Time fee to Deposition Account No. 07-1896. No other fee is believed to be due in connection with this submission. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,



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